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ALDOSTERONE, ANTIDIURETIC HORMONE AND CONGESTIVE HEART FAILURE*

The *precise* mechanisms by which edema formation takes place during the development of congestive cardiac failure are unknown. The hormonal aspects, however, have recently come to attention and appear to hold the key to an improved understanding of the several physiological adjustments of the body which are involved. In this brief discussion of the endocrine factors taking part in the development of cardiac edema, we shall attempt to correlate and interpret the available knowledge in a way that appears reasonable to us at the present time.

In fully developed congestive heart failure with edema, the following conditions obtain:

1. Total body exchangeable sodium is increased.[1]
2. Extracellular fluid volume, as well as total body water, are increased.[2]
3. Renal tubular reabsorption of sodium and water is excessive.[3, 4]
4. Production and excretion of aldosterone are excessive.[5-8]
5. Antidiuretic hormone (ADH) activity is increased.[9-13]

Even when cardiac compensation has been established and the so-called edema-free state exists, urinary aldosterone excretion, although diminished from its former levels, remains abnormally high[14, 15] and elevation of the total exchangeable body sodium persists.[1] Studies of Barger, *et al.*,[16, 17] indicate: (*a*) that renal retention of sodium is one of the earliest manifestations of mild circulatory incompetence; (*b*) that such renal retention of sodium precedes any measurable rise in venous pressure; and (*c*) that it takes place before any decrease in glomerular filtration rate is observed. Under such conditions, however, there is a decrease in renal plasma flow and it is possible that a significant decrease of glomerular filtration rate, not detectable by present methods,[18] has occurred.

In any case, it is quite evident that although circulatory incompetence is the initiating factor, the kidney is responsible for impeding the normal excretion of sodium.

Some of the major systems which appear to operate in the development of congestive heart failure with edema are as follows:

1. **Heart**
   Decreased *effective* cardiac output
2. **Vascular System**
   Increased venous blood volume and pressure
   Transudation
   Decreased volume, pressure or blood flow in all or in a portion of the arterial circulation
   Arterial receptor center through which production of ASH (aldosterone-stimulating hormone) is reflexly increased via a hypothalamic center
3. **Adrenal Cortex**
   Increased secretion of aldosterone (independent of pituitary ACTH) in response to ASH
4. **Kidney**
   Decreased renal plasma flow
   Early—no detectable decrease of GFR (glomerular filtration rate)
   Late—severe decrease in GFR
   Increased tubular reabsorptive capacity for sodium
   Before, as well as after, an increase of venous pressure can be demonstrated
   Persistence of normal reabsorptive capacity for water
   Normal responsiveness to endogenous and exogenous ADH (antidiuretic hormone)

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5. **Hypothalamic — Posterior Hypophyseal System**
   Early congestive failure—no abnormality of ADH production or degradation
   Late—increased ADH release independent of osmoreceptor control

Obviously, one must begin the story with circulatory incompetence and attempt to trace the mechanisms by which the kidney prevents the normal urinary excretion of sodium and water. In the past, it was believed that the decreased GFR which accompanies severe congestive heart failure was wholly responsible for the retention of sodium within the body.[19, 20] Assuming a constant renal tubular reabsorptive capacity for sodium, the diminished filtered load of sodium was thought to be almost completely reabsorbed without requiring any change in tubular activity. It soon became evident, however, that while this mechanism contributes importantly to total sodium retention, it fails to explain many observations, including the fact that the GFR is normal in some patients with congestive heart failure and edema. It has been shown, for example, that hypophysectomy[21] or constriction of the renal artery,[22] either of which produces chronic reduction of the glomerular filtration rate, do not result in edema or in positive sodium balance.

In cirrhotics with ascites,[23] and in nephrotics with edema,[24] the GFR is very often above normal. Farnsworth[25] has reported some cardiac patients in whom the GFR has continued to be low during diuresis and in whom it has increased during the formation of edema. The sodium depleted dog retains administered sodium maximally even as the glomerular filtration rate is rising.[26] When hypertonic saline is injected directly into the renal artery of a normal dog, a sharp increase of sodium excretion occurs without any changes in creatinine and para-aminohippurate clearance or in sodium excretion from the opposite kidney. When this same experiment is carried out in a dog with frank congestive failure, no increase in sodium excretion occurs. This is true even when the GFR is normal and when, therefore, the infused sodium has been presented directly to the kidney tubules.[18]

One must conclude, therefore, that while the GFR is important as a mechanism of sodium retention, increased tubular reabsorption of sodium appears to be the mechanism which is called into play at a much earlier time in the course of the development of congestive cardiac failure. There can be little doubt that this increased tubular activity for reabsorption of sodium is induced by the presence of increased amounts of aldosterone. The next problem, then, involves the mechanism by which an incompetent circulatory system brings forth increased adrenal production of aldosterone.

Large doses of ACTH given to normal people produce mild increases in urinary aldosterone.[27] Under these circumstances, the levels of urinary aldosterone are considerably lower than those observed in patients with congestive heart failure or in normal people under conditions of sodium restriction.[4] Furthermore, the mild increases of urinary aldosterone observed with ACTH administration are accompanied by large increases in 17-ketosteroids and in 17-hydroxycorticosteroids.[27] In congestive heart failure, the normal values for 17-ketosteroids and 17-hydroxycorticosteroids in the presence of markedly elevated aldosterone levels eliminates endogenous pituitary ACTH as the mechanism of action.

Potassium loading has been shown to lead to a mildly increased excretion of aldosterone.[28, 29] This occurs without any increase in 17-hydroxycorticosteroids or 17-ketosteroids and, therefore, acts through a mechanism other than pituitary ACTH. However, there is nothing to suggest that the increase in aldosterone which occurs in congestive heart failure is related to this mechanism.

The most likely stimulus to increased secretion of aldosterone in congestive heart failure appears to involve a "dislocation" or abnormal redistribution of extracellular fluid. The receptor is probably located on the arterial side of the vascular system and may be responsive to changes in volume, pressure or blood flow. Evidence available for these presumptions may be summarized as follows:

1. When blood volume is diminished in normal people by bleeding, urinary aldosterone rises. This is true even when the volume of blood removed is replaced with saline containing the amount of sodium previously removed with the blood. On the other hand, when the donor's blood cells plus salt-poor albumin are reinfused, urinary aldosterone falls.[30]

2. Similarly, in a patient with hypoproteinemia, edema, and high urinary aldosterone, expansion of the intravascular compartment by administration of salt-poor albumin intravenously leads to a sharp decrease in urinary aldosterone, together with a marked increase in urinary sodium.[30]

3. Sodium restriction in normal people results in a great increase in aldosterone.[4] When such individuals are given a large water load, together with intramuscular pitressin, great hemodilution occurs and there is a sharp fall of urinary aldosterone.[31] It is significant, too, that under these circumstances urinary aldosterone falls at the same time that the concentration of sodium in the serum is falling. These and other experiments make it clear that the sodium concentration within the body is not a critical factor in the regulation of aldosterone secretion. Rather, it appears that changes in intravascular volume produce

changes in the adrenal secretion of aldosterone.

One is justified in stating that in congestive heart failure, *effective* blood volume and *effective* cardiac output are diminished even when total blood volume and total extracellular fluid volume are increased greatly above normal. Barger[18] pointed out that a number of circulatory stresses, such as the sequestration of blood in the extremities by venous occlusive cuffs, mild hemorrhage, the development of edema in chronic anemia, and the increased sodium excretion that occurs upon closure of an arteriovenous anastomosis, all give evidence that a tendency for decreased arterial filling is associated with sodium and water retention. Elkinton[32] suggested that a reduction in renal blood flow is capable of lowering sodium excretion by producing a change in tubular reabsorption of sodium. The two phenomena are undoubtedly related and involve increased activity of aldosterone, but no one has yet been able either to locate or to determine the nature of the vascular-receptor mechanism which reflexly makes known the need for increased amounts of aldosterone. Intracranial "volume receptors" within the vascular system have been suggested as possible regulators of sodium and water excretion, but the evidence is not yet strong. However, the recent work of Farrell, *et al.*,[33] on the "Diencephalic Regulation of Aldosterone Secretion" appears to be important as it concerns the hypothalamic site of the production of aldosterone-stimulating hormone. This does not necessarily place the "vascular receptor" within the skull.

On the basis of their recent work upon experimental congestive heart failure and experimental ascites in the dog, Davis, *et al.*,[8] suggest that hepatic venous congestion, the increased permeability of hepatic vascular and lymphatic beds from which fluids and electrolytes escape readily from the blood stream, and the consequent effect of this fluid loss upon the circulation as a whole may be the order of events which leads to increased secretion of aldosterone. These workers also found by analysis of adrenal venous blood that dogs with heart failure secrete approximately six times as much aldosterone per hour as do normal dogs. These findings of greatly increased *production* of aldosterone in congestive heart failure tend to minimize the importance of a postulated impaired hepatic degradation and conjugation of aldosterone,[34] although they do not eliminate this possibility as being contributory.

It seems likely to us that the very earliest phase of sodium retention during the development of congestive heart failure will prove to be due to transudation of fluid, unaccompanied by either increased aldosterone secretion or increased renal tubular reabsorption of sodium. Very soon, however, the "leak" and its consequent effects upon the "arterial receptor mechanism" brings forth a reflex increase in aldosterone secretion. Under many circumstances, such as loss of fluid by sweating, this mechanism quickly repairs the circulatory incompetence and thus turns itself off. Where myocardial weakness is the primary defect, it is probable that the mechanism (reflex stimulation of increased aldosterone production) once provoked *must* persist to some degree unless the primary defect is corrected or disappears. This is to say that in the early phases of cardiac insufficiency, *circulatory* efficiency may actually be maintained at its best possible level for long periods of time by virtue of a mild increase of aldosterone activity. Sodium balance would then be established at a new level of aldosterone output which initially was responsible for adding some sodium and water to the body, but now is required to hold it there. Such a concept is consistent with the following observations:

1. Increased exchangeable sodium is known to be present in the state of so-called cardiac compensation.
2. Chronic administration of mineralo-corticoids to normal people results in transient retention of sodium and water. Sodium and water are added to the body but further positive balance for these substances ceases, despite continued administration of the sodium-retaining steroid. In fact, under these circumstances one sometimes observes a diuresis of some of the sodium and water that has been retained initially.
3. Severely decompensated cardiacs with very high values for urinary aldosterone still maintain elevated levels (although much lower) after "compensation" has been established.

However, as the heart fails progressively, the aldosterone mechanism is activated more intensely in step-wise fashion. The purpose for which this compensatory mechanism is progressively activated may be accomplished in part but never fully. The accumulation of massive edema becomes a by-product of a mechanism designed to aid a failing myocardium in maintaining the best possible degree of circulatory efficiency for the longest possible time.

When one interferes with this mechanism for partial compensation by inducing natruresis and providing a diet containing very little sodium, the early response is loss of water along with sodium and maintenance of normal osmolarity of the extracellular fluid.[35] This means, however, that the total extracellular fluid volume has been reduced with a concomitant *further* reduction of volume, pressure or plasma flow at the critical "arterial receptor" area. Because of a lack of available sodium, the aldosterone mechanism, although continuously activated, is rendered virtually ineffective. It is at this point that a paradox occurs. The ability to excrete a water load decreases sharply, dilution hyponatremia occurs,

and urinary specific gravity rises. There seems little doubt that this phenomenon constitutes a "last ditch" stand to preserve a semblance of effective circulating volume by increased liberation of ADH, the latter despite induction and continuation of hypo-osmolarity of the extracellular fluid.[9] All are aware of the difficulties in clinical management which this situation presents.

The simple concept seems valid that any changes of function of endocrine glands which result from extraglandular abnormalities (secondary glandular hyper- and hypofunction) are compensatory and, therefore, purposeful. In the case of the failing heart, the compensatory mechanisms are directed at maintaining the best possible "effective circulating blood volume" and the eventual by-product is gross edema. A precarious balance is established with a progressively diminishing margin of safety in which either a slight degree of overcompensation, or a slight decrease in effective cardiac output, can quickly compromise circulatory efficiency and result in acute renal retention of salt and water.

The absence of edema in patients with primary aldosteronism,[36] as contrasted with patients who have congestive heart failure and secondary aldosteronism, may find its explanation in the following phenomena:

1. The patient with primary aldosteronism exhibits pitressin resistance. Hyposthenuria or isosthenuria, polyuria, and polydipsia are characteristic. These manifestations are the effects upon renal function of chronic depletion of potassium.[37, 38]

2. The rarity of kaliopenia in congestive heart failure with secondary aldosteronism may be due to the inability to increase the GFR. A load of sodium sufficiently large to bring about potassium depletion never reaches the distal tubule for exchange with potassium. Thus, the patient with primary aldosteronism, because of a heart which is capable of making the circulatory adjustment, goes on to kaliopenic nephropathy with its attendant decreased capacity to reabsorb water. In addition, he establishes a new equilibrium in which sodium balance is maintained at a high level of aldosterone secretion after total body exchangeable sodium has been increased. This latter phenomenon is very similar to the state of affairs as it exists in normal or adrenalectomized dogs treated chronically with large doses of desoxycorticosterone.[39, 40] On the other hand, when the same type of experiment is performed on adrenalectomized animals with previously induced congestive heart failure, sodium retention becomes virtually complete and massive ascites ensues.[41]

Although progress is obviously being made, more information is needed before all of the mechanisms involved in the complex syndrome of congestive heart failure can be placed in proper perspective in relation to each other.

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